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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,621	02/08/2002	Peter B. Reiner	100103.402	3213

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	9

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/072,621	REINER ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sh t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *6 and 15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group 1b (claims 1-5 and 7-15) in Paper No. 8 (30 May 2003) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Concerning the restriction requirement, the restriction between SEQ ID NO's as set forth at pp. 3-4 ¶3 in the previous Office Action (Paper No. 6, 18 November 2002) is hereby *withdrawn*.

3. Claims 1-5 and 7-15 are under examination as they pertain to ABCB9, ABCG4, and ABCG1 and wherein the ABC transporter is contacted with a small molecule.

Drawings

4. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figure 1. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

5. Claims **7** and **13** are objected to because of the following informalities: recite non-elected material. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims **1-5, 7, 14,** and **15** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

7. The claims are drawn very broadly to a method of regulating expression of amyloid precursor protein in a cell said method comprising regulating expression of an ABC transporter wherein a small molecule is used. The language of said claims encompasses both *in vivo* and *in vitro* methods.

8. The Specification teaches that ABCB9 increases APP expression. WT6 cells (293-EBNA cells stably transfected with APP^{wt}) transfected with ABCB9 demonstrate increase APP expression levels as determined by SDS-PAGE analysis (pp. 6; Example 1-3). WT6 and SM4 cells (293 EBNA cells stably transfected with Swedish mutant APP-695 mutant) transfected with ABCG4 showed increase APP695 expression but the same cells transfected with mutant ABCG4 (taken by the Examiner to be non-functional muteins) did not show any increase in APP695 expression (pp. 7). The Specification asserts that similar results were found with ABCG1.

9. The specification fails to provide any guidance for the successful regulation of ABC transporter expression, and since resolution of the various complications in regards to targeting the role a particular gene in amyloid precursor protein expression is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known amyloid precursor protein (APP) expression regulators to correlate with ABC transporter levels. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

10. Since the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using as of yet unspecified small molecules to regulated the expression of ABC transporters and thus regulate the expression of APP. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a small molecule *in vivo* based solely on *in vitro* transfection studies is highly problematic (see MPEP 2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed method in *in vivo* therapeutic methods, such a disclosure would not be considered enabling since the state of APP is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

11. The following references are cited herein to illustrate the state of the art of APP.

12. Concerning the nature of the invention, Lam *et al.* (February 2001) "β-Amyloid efflux mediated by p-glycoprotein." Journal of Neurochemistry **76**(4): 1121-1128 teaches that p-glycoprotein (p-gp), a member of the ABC transporter family, is an $A\beta_{1-40}$ and $A\beta_{1-42}$ transporter (Figure 3). Further, Lam *et al.* teaches that inhibition of p-gp with RU486 and RU49953 reduces Aβ secretion (Figure 2). It is noted that this satisfies a limitation of claim 8, wherein the activity of an ABC transporter is regulated, as inhibition is a form of regulation. However, the expression of Aβ was not affected *per se*, but the secretion (pp. 1127). This evidence is to the nature of the claims because Aβ secretion is regulated, as a reduction is a form of regulation, but not expression.

13. On the breadth of the claims, Schmitz *et al.* (2001) "Role of ABCG1 and other ABCG family members in lipid metabolism." Journal of Lipid Research **42**: 1513-1520 teaches that ABCG1 and ABCG4 are widely expressed but does not detail that they have been found in the nervous system, specifically the brain. Further, other ABCG family members are concentrated in the small intestine and liver. Thus the breath of the claims is not supported by the expression pattern of ABCG family members.

14. Concerning the nature of the invention, Koldamova *et al.* (11 April 2003) "*22R*-Hydroxycholesterol and 9-*cis*-Retinoic Acid Induce ATP-binding Cassette Transporter A1 Expression and Cholesterol Efflux in Brain Cells and Decrease Amyloid β Secretion." The

Journal of Biological Chemistry **278**(15): 13244-13256 teach that treatment of cultures of primary neurons, primary microglia, and astrocytes with *22R*-hydroxycholesterol and 9-*cis*-retinoic acid induced ABCA1 expression and increased apoA-I-mediated cholesterol efflux, consequently decreasing cellular cholesterol content. This lead to a concomitant decrease in $A\beta_{1-40}$ and $A\beta_{1-42}$ levels (Figures 8-10). While not discounting the possible contribution of other factors, Koldamova *et al.* did demonstrate a nexus between increasing mRNA levels of ABCA1 and a reduction of $A\beta_{1-40}$ and $A\beta_{1-42}$ levels *in vitro* (pp. 13255). However, the Specification as filed lacks support for the use of *22R*-hydroxycholesterol and 9-*cis*-retinoic acid in increasing or inducing ABC transporter expression. Thus there is not sufficient guidance to support the claims in light of Koldamova *et al.*'s study.

15. On the prior art, Venkateswaran *et al.* (12 May 2000) "Human White/Murine ABC8 mRNA Levels Are Highly Induced in Lipid-loaded Macrophages." The Journal of Biological Chemistry **275**(19): 14700-14707 teach that specific oxysterols including 25-, 20(*S*)-, and 22(*R*)-hydroxycholesterol induce ABC8 expression (Figures 3-5) and Venkateswaran *et al.* (24 October 2000) "Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXRα." PNAS 97(22): 12097-12102 teaches that oxysterols induce ABCA1 expression (Figure 1). Thus the skilled artisan is provided support for using oxysterols but as such it is not clear whether use of oxysterols while inducing ABC transporter expression will directly effect APP expression.

16. On the predictability of the invention, Schmitz & Kaminski (August 2002) "ABCA2: a candidate regulator of neural transmembrane lipid transport." Cell Mol Life Sci. **59**(8): 1285-1295 teaches that unlike other ABC A-subfamily members, ABCA2 is predominantly expressed in the brain and neural tissues. Thus the skilled artisan is confronted with a level of

unpredictability whether an ABC transporter as claimed, ABCB9, ABCG4, or ABCG1 will be present in neuronal tissues and thus capable of effecting APP expression.

17. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* regulating of APP expression via ABC transporter expression as exemplified in the references herein.

18. Claims **8-15** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

19. The claims are drawn very broadly to a method of regulating expression of amyloid precursor protein in a cell said method comprising regulating activity of an ABC transporter with a small molecule. The language of said claims encompasses both *in vivo* and *in vitro* methods.

20. The Specification teaches that ABCB9 increases APP expression. WT6 cells (293-EBNA cells stably transfected with APP^{wt}) transfected with ABCB9 demonstrate increase APP expression levels as determined by SDS-PAGE analysis (pp. 6; Example 1-3). WT6 and SM4 cells (293 EBNA cells stably transfected with Swedish mutant APP-695 mutant) transfected with ABCG4 showed increase APP695 expression but the same cells transfected with mutant ABCG4 (taken by the Examiner to be non-functional muteins) did not show any increase in APP695 expression (pp. 7). The Specification asserts that similar results were found with ABCG1.

21. The specification fails to provide any guidance for the successful regulation of ABC transporter activity, and since resolution of the various complications in regards to targeting the role a particular gene in amyloid precursor protein (APP) expression is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known amyloid precursor protein (APP) expression regulators to correlate with ABC transporter activity. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

22. Since the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using as of yet unspecified small molecules to regulated the activity of ABC transporters and thus regulate the expression of APP. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a small molecule *in vivo* based solely on *in vitro* transfection studies is highly problematic (see MPEP 2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed method in *in vivo* therapeutic methods, such a disclosure would not be considered enabling since the state of APP is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;

(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

23. The following references are cited herein to illustrate the state of the art of APP.

24. Concerning the nature of the invention, Lam *et al.* (February 2001) "β-Amyloid efflux mediated by p-glycoprotein." Journal of Neurochemistry **76**(4): 1121-1128 teaches that p-glycoprotein (p-gp), a member of the ABC transporter family, is an $A\beta_{1-40}$ and $A\beta_{1-42}$ transporter (Figure 3). Further, Lam *et al.* teaches that inhibition of p-gp with RU486 and RU49953 reduces Aβ secretion (Figure 2). It is noted that this satisfies a limitation of claim 8, wherein the activity of an ABC transporter is regulated, as inhibition is a form of regulation. However, the expression of Aβ was not affected *per se*, but the secretion (pp. 1127). This evidence is to the nature of the claims because Aβ secretion is regulated, as a reduction is a form of regulation, but not expression.

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Expression and Cholesterol Efflux in Brain Cells and Decrease Amyloid β Secretion." The Journal of Biological Chemistry **278**(15): 13244-13256 teach that treatment of cultures of primary neurons, primary microglia, and astrocytes with *22R*-hydroxycholesterol and 9-*cis*-retinoic acid induced ABCA1 expression and increased apoA-I-mediated cholesterol efflux, consequently decreasing cellular cholesterol content. This lead to a concomitant decrease in $A\beta_{1-40}$ and $A\beta_{1-42}$ levels (Figures 8-10). While not discounting the possible contribution of other factors, Koldamova *et al.* did demonstrate a nexus between increasing mRNA levels of ABCA1 and a reduction of $A\beta_{1-40}$ and $A\beta_{1-42}$ levels *in vitro* (pp. 13255). However, the Specification as filed lacks support for the use of *22R*-hydroxycholesterol and 9-*cis*-retinoic acid in increasing or inducing ABC transporter expression. Thus there is not sufficient guidance to support the claims in light of Koldamova *et al.*'s study.

27. On the prior art, Venkateswaran *et al.* (12 May 2000) "Human White/Murine ABC8 mRNA Levels Are Highly Induced in Lipid-loaded Macrophages." The Journal of Biological Chemistry **275**(19): 14700-14707 teach that specific oxysterols including 25-, 20(*S*)-, and 22(*R*)-hydroxycholesterol induce ABC8 expression (Figures 3-5) and Venkateswaran *et al.* (24 October 2000) "Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXRα." PNAS 97(22): 12097-12102 teaches that oxysterols induce ABCA1 expression (Figure 1). Thus the skilled artisan is provided support for using oxysterols but as such it is not clear whether use of oxysterols while inducing ABC transporter expression will directly effect APP expression.

28. On the predictability of the invention, Schmitz & Kaminski (August 2002) "ABCA2: a candidate regulator of neural transmembrane lipid transport." Cell Mol Life Sci. **59**(8): 1285-1295 teaches that unlike other ABC A-subfamily members, ABCA2 is predominantly expressed

in the brain and neural tissues. Thus the skilled artisan is confronted with a level of unpredictability whether an ABC transporter as claimed, ABCB9, ABCG4, or ABCG1 will be present in neuronal tissues and thus capable of effecting APP expression.

29. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* regulating of APP expression via ABC transporter activity as exemplified in the references herein.

30. Claims **1-5** and **7-15** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

31. The claims are drawn a method of using a small molecule to regulate expression or regulate activity of an ABC transporter. The claims do not require that the small molecule possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of small molecule that is defined by to broad activities, regulating expression and/or activity of the large genus of ABC transporters.

32. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the

claim that is sufficiently disclosed is broad activities, regulating expression and/or activity of the large genus of ABC transporters. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. No adequately described species is taught by the instant Specification. Accordingly, the specification does not provide adequate written description of the claimed genus.

33. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of small molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

34. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

35. Therefore, no representative members of a genus or particular small molecule of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

36. Claims **1, 7, 8,** and **13** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

37. The term "regulating" in claims **1, 7, 8,** and **13** is a relative term which renders the claim indefinite. The term "regulating" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear from the instant Specification as to the metes and bounds of what constitutes "regulation" or is necessary to fulfill the preamble.

38. Claims **1-12** are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how ABC expression is regulated and what agents are used to perform said regulation.

Summary

39. Claims 1-5 and 7-15 are hereby rejected.

40. It is noted that the Examiner has rejected claims 14 and 15 twice under 35 U.S.C. §112 ¶1. This is due to the fact that claim 14 is a multiple dependent claim of both independent claims 1 and 8. Thus claim 14 must be included in the rejection of both claim 1 and 8 as they represent different embodiments of the same invention. Claim 15 is also included in both rejections because it depends form 14, which in turns depends on both 1 and 8.

41. The following articles, patents, and patent publications were found by the Examiner during the prior art search and are here made of note:

a. Khovidhunkit *et al.* (1 July 2003) "Endotoxin Downregulates ABCG5 and ABCG8 in Mouse Liver and ABCA1 and ABCG1 in J774 Murine Macrophages: differential role of LXR." J Lipid Res. [Epub ahead of print]

b. US 6514686 B2 (4 February 2003) Reiner and Lam

c. US Patent Application Publication US 2002/0037843 A1 (28 March 2002) Reiner and Lam

d. US Patent Application Publication US 2002/0192821 A1 (19 December 2002) Reiner *et al.*

e. WO 98/48784 (5 November 1998) Reiner *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
August 7, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600